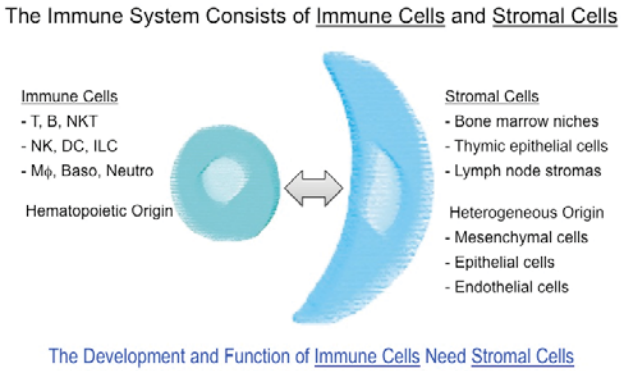
Title of Project : Analysis and synthesis of multidimensional immune organ network

Yousuke Takahama
(University of Tokushima, Institute for Genome Research, Professor)

【Purpose of the Research Project】

The development and function of immune cells depend on the systemic network of specialized microenvironments in immune organs, including the bone marrow, thymus, lymph nodes, and spleen. Although immune cells are of hematopoietic origin, the microenvironments of the immune organs are primarily formed from highly heterogeneous stromal cells of nonhematopoietic origins. Thus, to understand the immune system, it is essential to elucidate how the stromal cells and their network develop and function normally and deviate during aging and in diseases. In this project, we focus on the studies of immune organ microenvironments by multidisciplinary approaches, including synthetic biology, towards the understanding of multidimensional characteristics of stromal cells and their coordinated network.



【Content of the Research Project】

This project consists of three research aspects as follows. In the first aspect of the study, we seek to understand the molecular mechanisms underlying the development and function of the bone marrow niches, thymic microenvironments, and stromal cells in secondary lymphoid organs. In the second aspect, we seek to clarify the dynamic regulation of the immune organ network through structural analysis and intravital imaging of immune molecules and stromal cells. In the third aspect, we seek to understand the deviations of immune organs caused by ageing and diseases and to reconstruct immune functions through synthetic approaches.

【Expected Research Achievements and Scientific Significance】

This study is expected to contribute to comprehensive understanding of the multidimensional nature of the dynamic immune system, functional interfaces of the immune system with the endocrine and nervous systems, and the nature of the “context” detected in various biological systems. Advances in the understanding of immune deviations and reconstruction of immune organ functions should be useful for devising novel approaches to the treatment and management of various intractable diseases.

【Key Words】 immune organ, stromal cell, microenvironment, systemic organ network, immune synthesis

【Term of Project】 FY2012-FY2016

【Budget Allocation】 1,129,400 thousand yen

【Homepage Address and Other Contact Information】

http://immuneorgannetwork.org
takahama@genome.tokushima-u.ac.jp

Title of Project : New aspect of the ubiquitin system : its enormous roles in protein regulation

Kazuhiro Iwai
(Kyoto University, Graduate School of Medicine, Professor)

【Purpose of the Research Project】

Since identified as part of the energy-dependent protein degradation system, ubiquitin has been regarded as a component of degradation machinery. However, the ubiquitin system is now known to play a wide variety of roles in protein regulation besides degradation. Various kinds of ubiquitin modifications, which are generated by polymerization of ubiquitin in different ways in most cases and are might be called as "ubiquitin code", are found in eukaryotic cells as illustrated in Figure 1. It has been hypothesized that types of ubiquitin modifications determine how the system regulates proteins. Also, most-advanced experimental techniques are now required to accomplish ubiquitin research with high-quality. It is almost impossible to conduct such all advanced techniques in one laboratory. In this innovative area research, therefore, researchers in the field of ubiquitin and various ubiquitin-related biological phenomena conduct ubiquitin research together and cooperatively develop new research techniques which are inevitably required for the progress of upcoming ubiquitin biology.

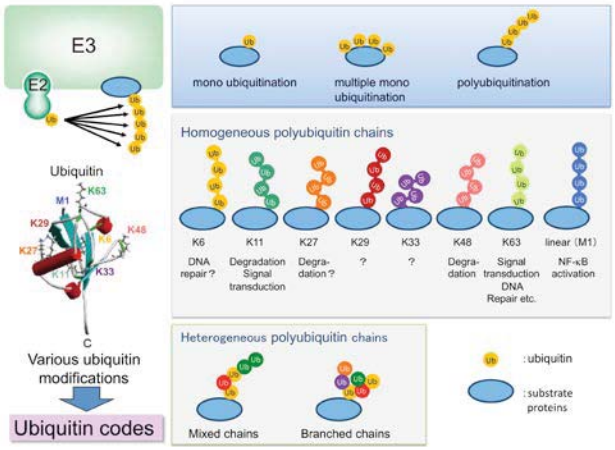


Figure 1. A wide variety of ubiquitin modifications and their biological roles

【Content of the Research Project】

In this research area, ubiquitin research in "post-degradation era" will be conducted from both functional and structural point of views.

1. In addition to conducting ubiquitin researches by fully utilizing research techniques and skills that we have already developed, we will develop new advanced techniques that are essential for future ubiquitin researches.

2. We will further dissect pathophysiological roles of the ubiquitin conjugation system by using newly developed research techniques.

【Expected Research Achievements and Scientific Significance】

1. We will establish world-leading advanced techniques to study ubiquitin and will clarify unidentified roles of the ubiquitin conjugation system in biology and medicine.

2. We believe that the outcomes of this research area (both biological achievements and technical development) will be beneficial to develop therapeutics to control the ubiquitin conjugation system and cure diseases including cancer.

【Key Words】

Ubiquitin, post-translational modifications and proteins

【Term of Project】 FY2012-2016

【Budget Allocation】 1,191,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://ubiquitin.jp

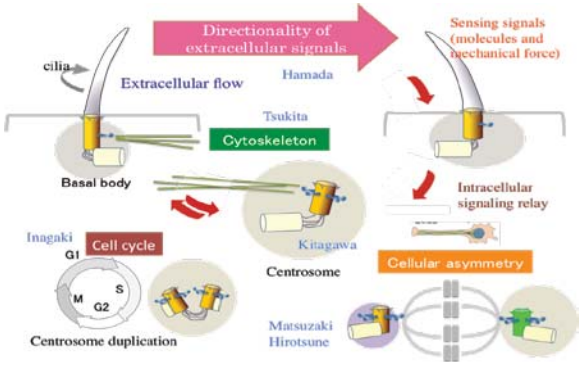
Title of Project : Cilium-centrosome system regulating biosignal flows

Hiroshi Hamada
(Osaka University, Graduate School of Frontier Biosciences, Professor)

【Purpose of the Research Project】

Centrosome serves as the microtubule organizing center during cell division. In quiescent cells, however, its core component centriole is transformed to basal body and functions as the basis of cilium formation. Cilia not only generate extracellular flow but also sense various extracellular signals, either molecules or mechanical force. In particular, primary cilium serves as a cellular antenna, and its defects result in a variety of human disorders (collectively called ciliopathy). In this project, we will consider the cilium and centrosome as a single cellular system that changes depending on cellular dynamics. By studying structure, dynamics and function of the cilium-centrosome system, we would like to understand how biosignal flows are regulated by the cilium-centrosome system.

【Content of the Research Project】



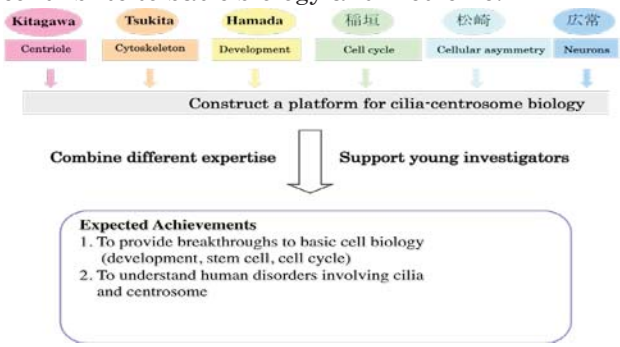
The cilium and centrosome have the common structure, the centriole. When cell cycle reaches G0/G1, the centrosome moves to the apical side of a cell. The mother centriole is transformed to the basal body, from which the cilium will be formed. Therefore, the centrosome and cilium are closely related organellas that changes mutually depending on the cell cycle. However, they have been treated as separate organellas.

In this project, we will treat the centrosome and cilium as a single system that changes dunamically and will study its role in cellular signaling. In particular, we will address the following issues.

1) Structures of the cilium, centrosome and centriole.
2) Interaction with cytoskeleton
3) How is the transition between the cilium and centrosome achieved and regulated?
4) How is the motility of the cilium regulated and how is the flow generated?
5) How does primary cilium senses extracellular signals such as biochemical signals and mechanical force?
6) How is cilium formation regulated by cell cycle?
7) How do centrosome/cilium-mediated signals regulate asymmetric cell division?
8) How does the centrosome/cilium system regulate neuronal activity?

【Expected Research Achievements and Scientific Significance】

This project will provide breakthroughs to basic cell biology, in various research fields such as development, stem cell, cell cycle. It will also help understanding the mechanisms underlying human disorders involving cilia and centrosome. In all, this project will greatly contribute to basic biology and medicine.



【Key Words】

Centrosome, cilium, cell cycle, asymmetric cell division

【Term of Project】 FY2012-2016

【Budget Allocation】 1,185,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.nig.ac.jp/labs/NigPrjct/cilia-centrosome/

Title of Project : The plant cell wall as information-processing system

Kazuhiko Nishitani
(Tohoku University, Graduate School of Life Sciences,
Professor)

【Purpose of the Research Project】

Although plants do not have a central nervous system like animals, individual plant cells have acquired highly autonomous capabilities in terms of information-processing. This autonomous cell system mediates whole-plant regulation and function. The cellular information-processing system constitutes the fundamental basis of major plant processes including growth, defense, and adaptation to the environment. However, the molecular mechanisms underlying plant information-processing systems are largely unknown. This research project specifically focuses on the cell wall, or apoplast, to gain insight into the information-processing system (Fig. 1), and attempts to dissect the molecular basis for plant-specific signal perception, processing, and responses. The project hypothesis is that, in addition to transcriptional regulation in the nucleus, apoplastic information-processing plays a critical role in regulating whole-plant function.

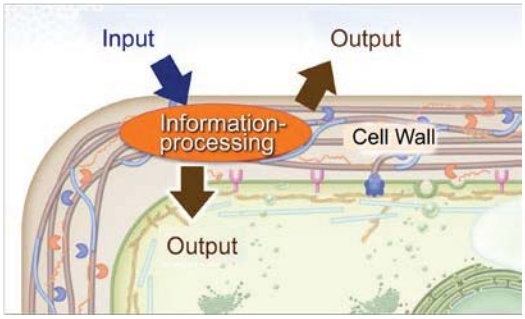


Fig. 1. Information-processing in the cell wall

The goal of this project is to explore the new area of apoplastic information-processing, which evolved independently in land plants. This work will establish a new approach to elucidating the still unknown high-order functions in land plants.

【Content of the Research Project】

This research consortium consists of three working groups (**A01**–**A03**) and nine principal investigators, whose original contributions to a wide spectrum of research fields in plant sciences have been outstanding. The tasks of each group are related but discrete: **A01** will elucidate the molecular mechanism(s) by which the cell wall space is constructed; **A02** will dissect cell wall function in terms of information-processing; and **A03** will determine how the cell wall functions as an interfacial zone in cell-to-cell and cell-to-environment interactions. The interaction between the three working groups is depicted in Fig. 2.

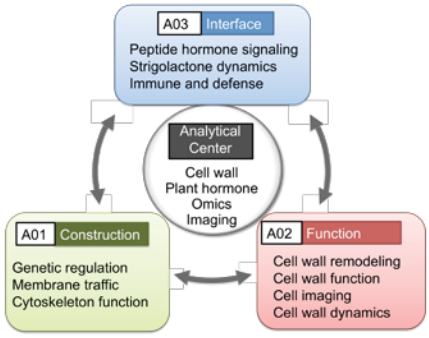


Fig. 2. Research groups and areas of focus

【Expected Research Achievements and Scientific Significance】

This project will pioneer novel approaches to understanding information-processing regulatory systems in plants, which are distinct from conventional transcription-based systems. Because plant cell walls comprise the largest fraction of the earth's biomass, their molecular dissection will enable a better understanding of global carbon resources. The project will contribute directly to human welfare and the development of science and technology.

【Key Word】

Plant cell wall: Plant extracellular super-structure, which is central to the regulation of plant growth and differentiation, immune defense, and response to the environment.

【Term of Project】 FY2012–2016
【Budget Allocation】 1,154,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.plantcellwall.jp/
nishitan@m.tohoku.ac.jp

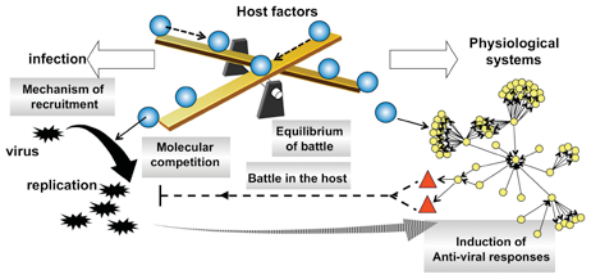
Title of Project : Molecular basis of host cell competency in virus infection

Kyosuke Nagata
(University of Tsukuba, Faculty of Medicine, Professor)

【Purpose of the Research Project】

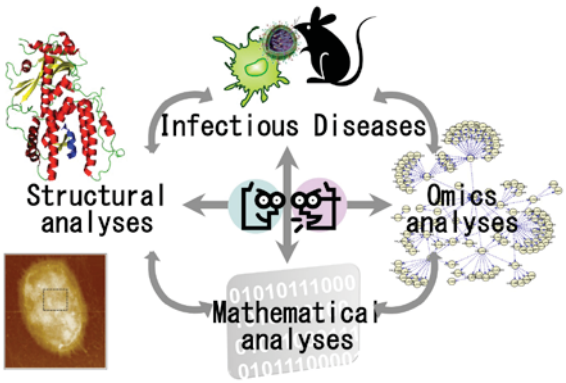
Viruses hijack and recruit various host factors for their replication processes. Thus, the virus proliferation depends on the availability of host factors and the compatibility of viral factors to their cognate host factors in species- and cell type-specific manners. Although cells induce anti-viral host defense systems in response to virus infection, the mechanism and the level of anti-viral state also vary in different species and cell types. Therefore, viral replication and pathogenicity are the consequence of the competition between viruses and host defense systems.

This project focuses to define the molecular basis of this competition in viral replication and pathogenicity as a concept of "host cell competency". The aim of our study is to clarify the molecular mechanisms of virus-host interaction and viral adaptation, that is, host range specificity and tissue- and cell type-specificity in virus infection.



【Content of the Research Project】

We will focus our studies on (1) competition between virus and host in cells, (2) competition between virus and host in animal bodies, and (3) consequence of the virus-host interaction and competition. By studying the interaction between viral and host factors, the competition mechanism between virus replication and anti-viral defense systems will be revealed. This will be accomplished by structural biology, omics analyses, and mathematical analyses in addition to virological techniques.



【Expected Research Achievements and Scientific Significance】

We expect to discover a new paradigm of "host cell competency" to forward the understanding of the molecular basis of viral pathogenesis, viral evolution, and viral adaptation to host. We also expect to develop new methods and concepts through collaboration with the experts in structural biology, omics analyses, and mathematical analyses. The outcome of this project may establish general principles on viral infection based on results obtained from mathematical modeling. Our project will make a greater contribution to control viral infection and facilitate development of viral vectors.

【Key Words】

Host cell competency: the ability of permitting viral replication by supplying host factors and the ability of inducing anti-viral host defense system.

【Term of Project】 FY2012-2016

【Budget Allocation】 1,024,100 Thousand Yen

【Homepage Address and Other Contact Information】

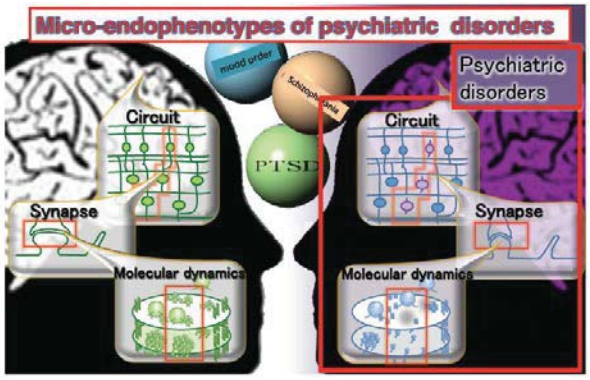
http://www.md.tsukuba.ac.jp/basic-med/infcompetence/
knagata@md.tsukuba.ac.jp

Title of Project : Unraveling the micro-endophenotypes of psychiatric disorders at the molecular, cellular and circuit levels.

Satoshi Kida
(Tokyo University of Agriculture, Faculty of Applied Bioscience, Professor)

【Purpose of the Research Project】

Psychiatric disorders are now one of the five major diseases in Japan; therefore, it is important to understand the mechanisms of these disorders and to develop therapeutic strategies. Importantly, the development of psychiatric disorders is not only due to genetic factors; rather they are strongly influenced by interactions between environmental and genetic factors. Furthermore, the mechanisms by which brain functions are controlled at the molecular, cellular, and circuit levels are still unknown. Therefore, unraveling the mechanisms of psychiatric disorders requires a variety of approaches including both basic and clinical studies. However, current collaborations between basic and clinical scientists are poorly organized as the endophenotypes of psychiatric disorders, which are their phenotypes at the psychological, physiological and behavioral levels, have not been studied sufficiently in basic research. Additionally, there are much less basic researchers studying psychiatric disorders in Japan compared to those in other fields of research such as cancer and metabolic syndromes. On the basis of this background, we will develop a new and innovative area studying psychiatric disorders, in which basic researchers using state-of-the-art techniques will collaborate with clinical researchers to use basic and clinical studies to understand psychiatric disorders. Especially, to develop basic research on psychiatric disorders, we propose to develop "micro-endophenotypes" that are the visualized phenotypes of psychiatric disorders at the molecular, cellular and circuit levels, as an interface between basic and clinical studies. We will identify micro-endophenotypes and understand their molecular basis.



【Content of the Research Project】

We will identify micro-endophenotypes using animal models and human materials such as iPS cells derived from patients and postmortem brains and then elucidate the molecular basis of micro-endophenotypes using state-of-the-art technologies. Our research team consists of three groups; A01, A02 and A03. Groups A01 and A02 focus on micro-endophenotypes at the molecular - cellular and circuit - behavioral levels, respectively, whereas group A03 focuses on micro-endophenotypes induced by environmental factors. In addition, we will develop new mouse models of psychiatric disorders that receive micro-infusions of iPS and iN cells derived from patients into the brain and analyze these mice. We will also develop state-of-the-art technologies to identify and analyze micro-endophenotypes.

【Expected Research Achievements and Scientific Significance】

Little progress has been made in unraveling phenotypes of psychiatric disorders at the molecular, cellular and circuit levels. Furthermore, the in vivo functions and dynamics of candidate molecules identified through genome-wide analyses of psychiatric disorders have not been well examined. The "micro-endophenotypes" proposed by our research group would be useful subjects for basic research and play crucial roles as an interface between basic and clinical studies of psychiatric disorders. Most importantly, the study of micro-endophenotypes in basic research would enable to the recruitment of Japanese basic researchers such as neuroscientists, molecular biologists, structural biologists and so on into the field of psychiatric disorders, and generate a new and strong research area to understand the molecular basis of psychiatric disorders in Japan.

【Key Words】
Micro-endophenotypes; the visualized phenotypes of psychiatric disorders at the molecular, cellular and circuit levels.

【Term of Project】 FY2012-2016

【Budget Allocation】 1, 135, 000 Thousand Yen

【Homepage Address and Other Contact Information】

http://microend.umin.ne.jp/
micro@nodai.ac.jp

Title of Project : Harmonized supramolecular motility machinery and its diversity

Makoto Miyata
(Osaka City University, Graduate School of Science,
Professor)

【Purpose of the Research Project】

The molecular mechanism of force generation by "conventional" motor proteins, e.g. myosin, kinesin, and dynein, is now fairly well understood after decades of research. However, many mechanisms of motility, including the surface and swimming motilities of bacteria and protozoa, cannot be explained using only conventional motor proteins. Such motilities are driven by highly organized structures, which we call "supramolecular motility machinery", and their diversity records the evolutional history of life on earth. Our research project will focus on these fascinating but poorly characterized motility mechanisms through studies from the atomic to the supramolecular-complex scales using cutting -edge analysis technologies.

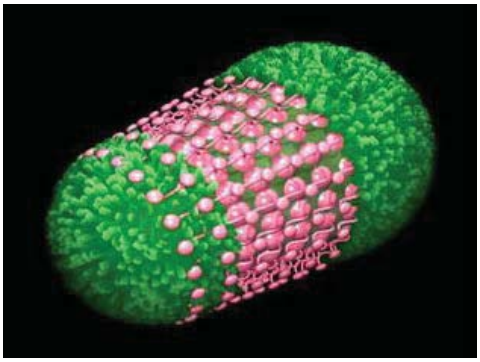


Figure 1　Cartoon of *Mycoplasma* cell surface (The supramolecular motility machinery is shown in pink)

【Content of the Research Project】

Researchers of supramolecular motility machineries working in different fields will come together and accelerate their studies based on multiscale methodology, including microbiology, genetics, biochemistry, biophysics, and structural biology. Our research project encourages studies of motility mechanisms which have not been characterized deeply as exploratory studies but also welcomes expert researchers on conventional motor proteins entering our field. Visualization techniques at the sub nanometer scales are critical for our field, and three of them, cryoelectron tomography, quick/freeze/replica electron microscopy, and fast scan AFM (atomic force microscopy) will be supported to develop applications for our studies. We will provide the latest information to both researchers and lay citizens effectively by stimulating interests in novel motilities and new platforms of multimedia.

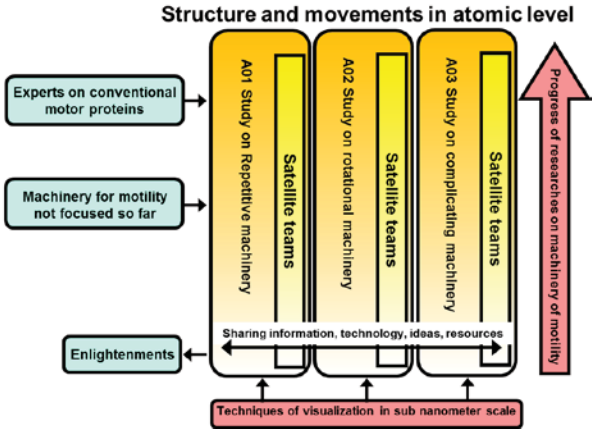


Figure 2　Overview of this research project

【Expected Research Achievements and Scientific Significance】

A concrete picture of various motility mechanisms will totally change our understanding of the motility of organisms and their evolutionary origins. Comparison of different mechanisms will allow us to understand the essence of motility, including the conventional motor proteins.

【Key Words】

Conventional motor proteins: The proteins responsible for force generation which have been studied extensively for a long time, including myosin, kinesin, and dynein. These proteins obtain energy through ATP hydrolysis and slide on actin filaments or microtubules.

【Term of Project】 FY2012-2016

【Budget Allocation】 1,162,600 Thousand Yen

【Homepage Address and Other Contact Information】

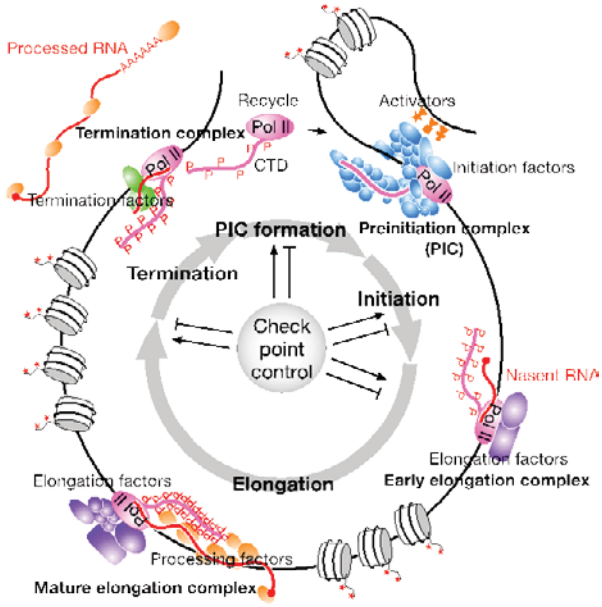
http://bunshi5.bio.nagoya-u.ac.jp/~mycmobile/index.html

Title of Project : Integral understanding of the mechanism of transcription cycle through quantitative, high-resolution approaches

Yuki Yamaguchi
(Tokyo Institute of Technology, Graduate School of Bioscience and Biotechnology, Associate Professor)

【Purpose of the Research Project】

The objective of this area is to elucidate the regulatory mechanism of "transcription cycle," and to thereby contribute to the understanding of complex physiological functions. The difficulty lies in a highly hierarchical structure of the processenvolved; due to technical limitations, each layer of research has been carried out individually, and the integration of resulting data has not been possible. In this area, we aim to gain an integrative perspective on multiple steps and layers of transcription using "high-resolution approaches," in which leading edge technology and computational science are combined with conventional methodology. A shift from qualitative to quantitative understanding and a shift from static to dynamic understanding would make it possible to understand the entire process of transcriptional regulation and to thereby contribute to the understanding of complex physiological functions.



【Content of the Research Project】

In this area, we will elucidate the remodeling cycle of transcription complexes, checkpoint control of transcription, and transcriptional regulation through gene looping; and thereby formulate the concept of "transcription cycle." Moreover, a deeper understanding of complex physiological functions will be gained through the integration of the transcription cycle of individual genes with those of each cell and organism using "high-resolution approaches." Specifically, leading-edge technology, including genome-wide analyses and new techniques for enabling kinetic and quantitative studies, will be developed and utilized. In addition, computer science will be fully utilized to process large datasets and to support kinetic studies. To promote the study on "transcription cycle," a research initiative will be established to perform single-molecule analysis in live cells, dynamic structural analysis, and genome-wide analyses using next-generation sequencers.

【Expected Research Achievements and Scientific Significance】

Our goal is not to draw nonquantitative models for transcriptional regulation, but to provide a precise, detailed view of it through quantitative, comprehensive analyses. This study is indispensible for the simulation and prediction of changes in gene expression through a systems biology approach in future and will contribute to genomic and epigenomic drug discovery.

【Key Words】

Transcription cycle: This is the term named after the similarity between transcription and cell cycle, and represents the entire process of transcription. Like cell cycle, transcription cycle is spatiotemporally controlled by external stimuli, and there are a number of checkpoints whose defects often result in developmental disorders or cancers. Moreover, some regulators indeed control both of these processes. Thus, cell cycle and transcription cycle are likely to support the basis for living organisms in a coordinated manner.

【Term of Project】 FY2012-2016

【Budget Allocation】 1,198,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://transcriptioncycle.org
yyamaguc@bio.titech.ac.jp